

# **A Selected History of Behavioral Clinical Trials: What Have We Learned?**

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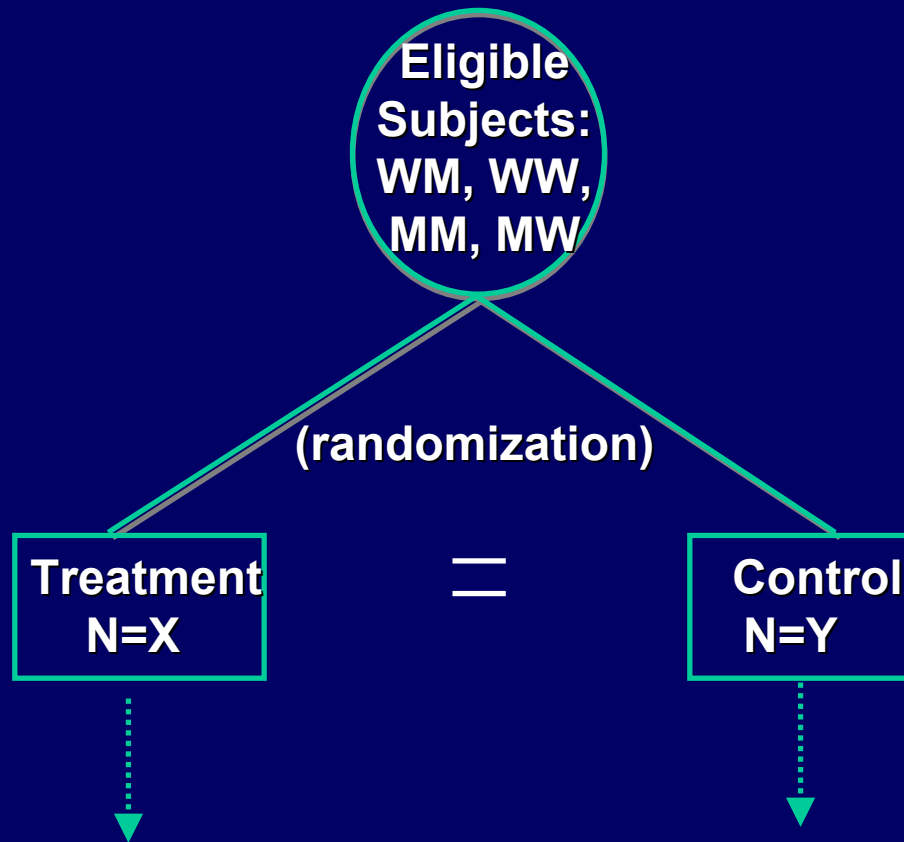
“The wrong view of science betrays itself  
in the craving to be right.”

Karl Popper,  
*The Logic of Scientific Discovery*, 1934

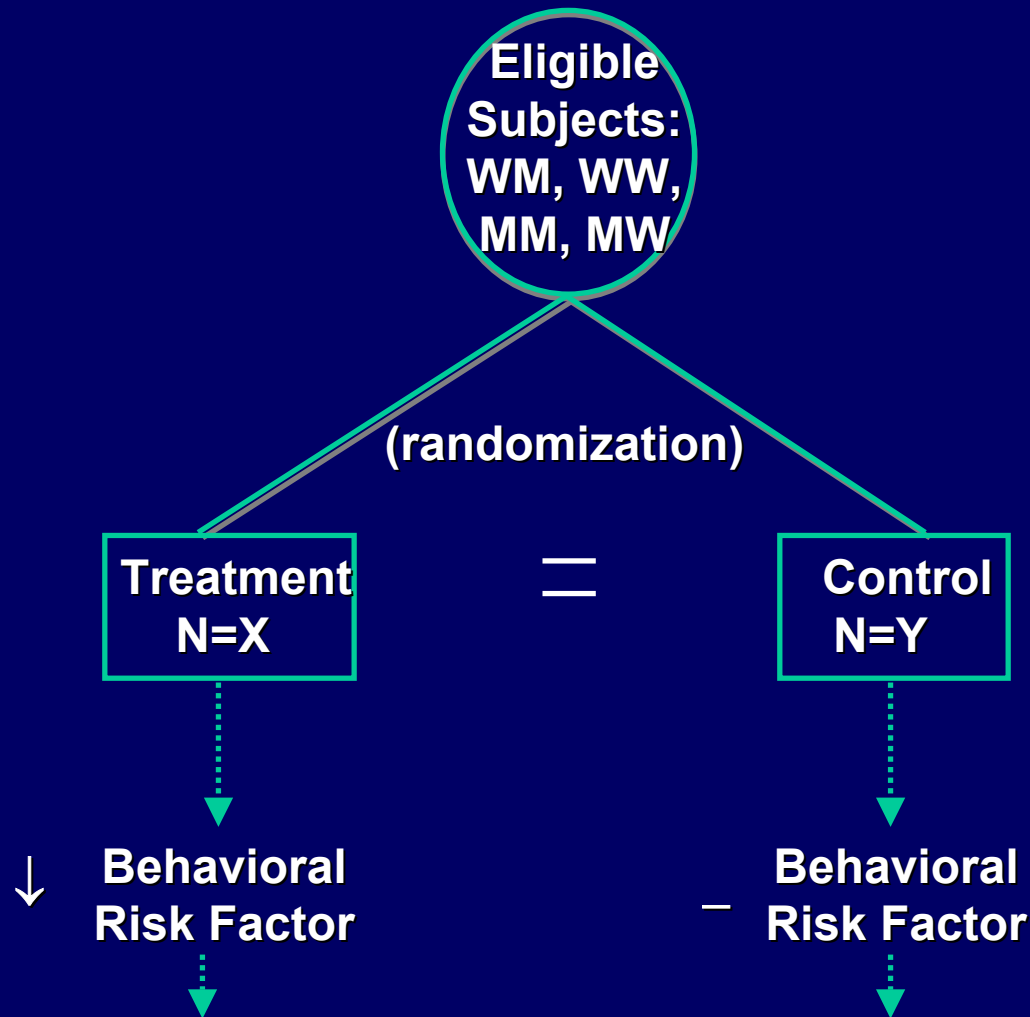
# Clinical Trial Design



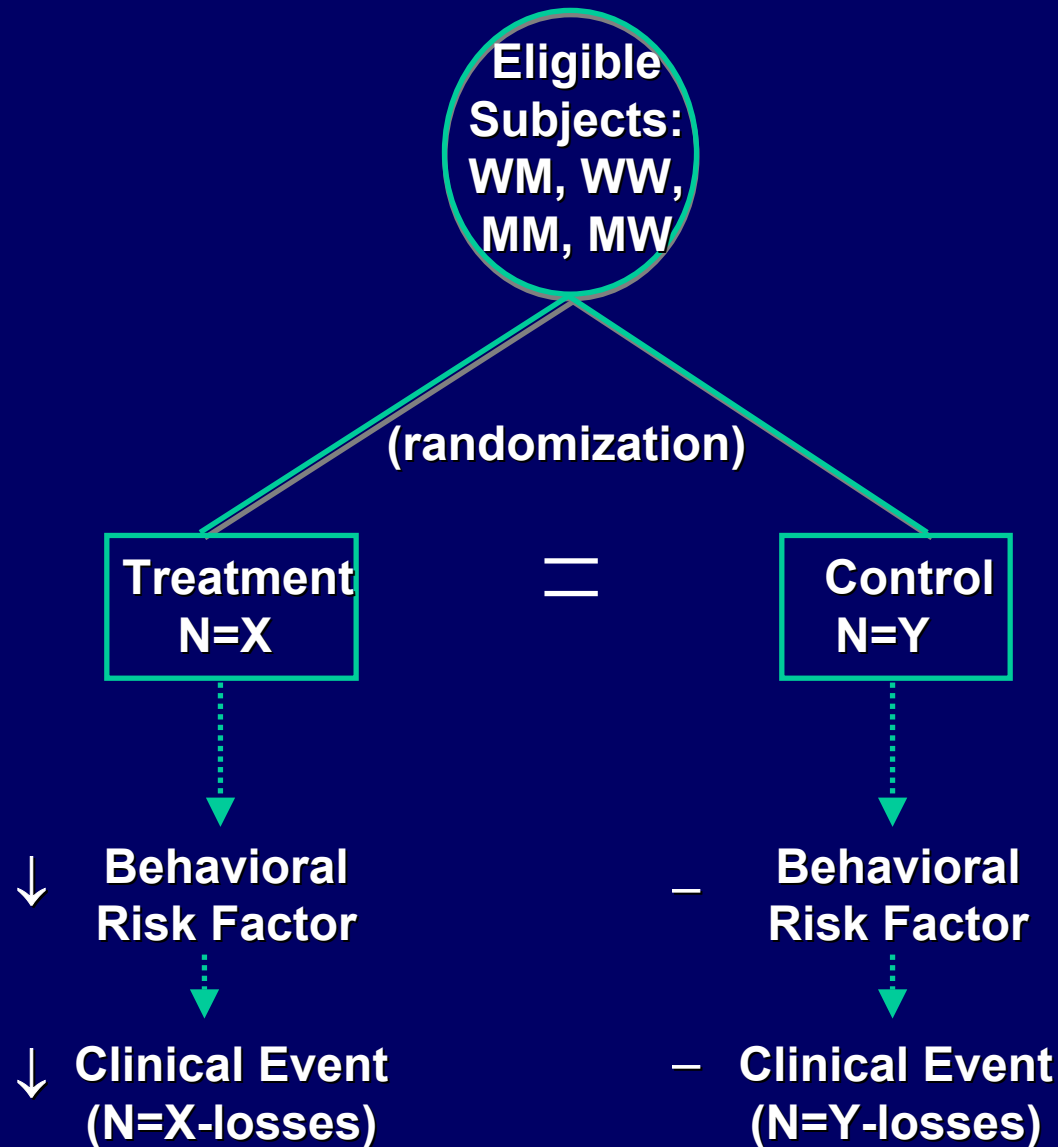
# Clinical Trial Design



# Clinical Trial Design

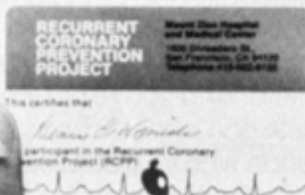


# Clinical Trial Design



TIME, JULY 17, 1979

# THIS CARD JUST MIGHT SAVE YOUR LIFE.



For every 100 people who have had one or more heart attacks, within five years 45% will have a second heart attack—and half of these people will die.

Frightening? You bet. These are alarming statistics. But something is being done to substantially reduce these odds, and it's being done in San Francisco.

Called the Recurrent Coronary Prevention Project, it's a program

currently underway at Mount Zion Hospital.

Earlier work done by the Mount Zion research group under the direction of Meyer Friedman, M.D., Director of the Harold Brunn Institute at Mount Zion Hospital and Medical Center, has shown that the number of fatalities from a second heart attack can be reduced from five out of

ten people to one out of ten.

If you have had a heart attack, here's what you can do. If you are currently a non-smoker, and do not suffer from diabetes, you are eligible to become a part of this program and receive your recurrent coronary prevention card which entitles you to all of the benefits of this project. There's no charge as the project is funded by the National Heart, Lung and Blood Institute.

**Act now  
before it's too late.**

For full details, call the  
RECURRENT CORONARY  
PREVENTION PROJECT  
**(415) 922-8155**

Typography:  
Ohrncomp, San Francisco

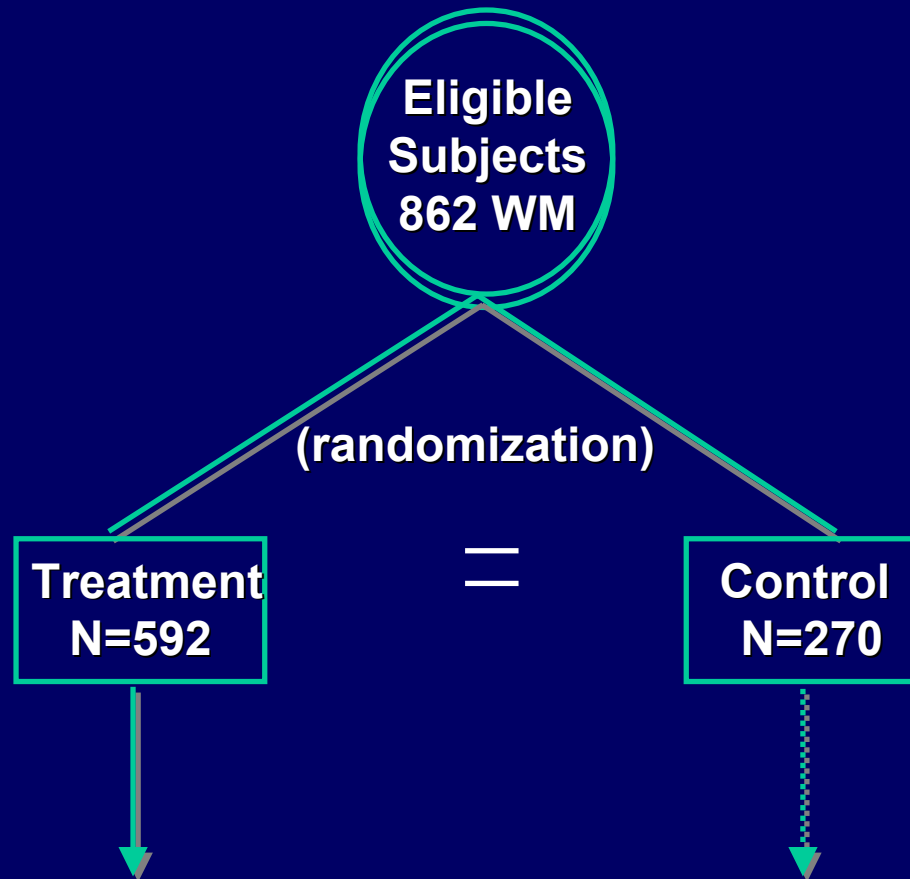
This ad prepared as a public service for the Recurrent Coronary Prevention Project  
by Scroggin, Reed Advertising, 843 Montgomery Street, San Francisco, California.

# The Recurrent Coronary Prevention Project 1977-1985

Principal Investigator: Meyer Friedman, MD

**PURPOSE:** To determine whether Type A behavior can be altered and, if so, the impact of such alteration on the incidence of cardiac death or nonfatal MI.

# RCPP Clinical Trial Design





Russell

*"If you can't relax, pretend to relax."*

I. 1. Walk more slowly than wife/friend

--	--	--	--	--	--	--	--

2. Speak more slowly

--	--	--	--	--	--	--	--

3. Eat more slowly

--	--	--	--	--	--	--	--

4. Discontinue fist clenching/knee jiggling

--	--	--	--	--	--	--	--

5. Leave watch off 2 of 5 working days

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6. Seek longest line in bank/shop

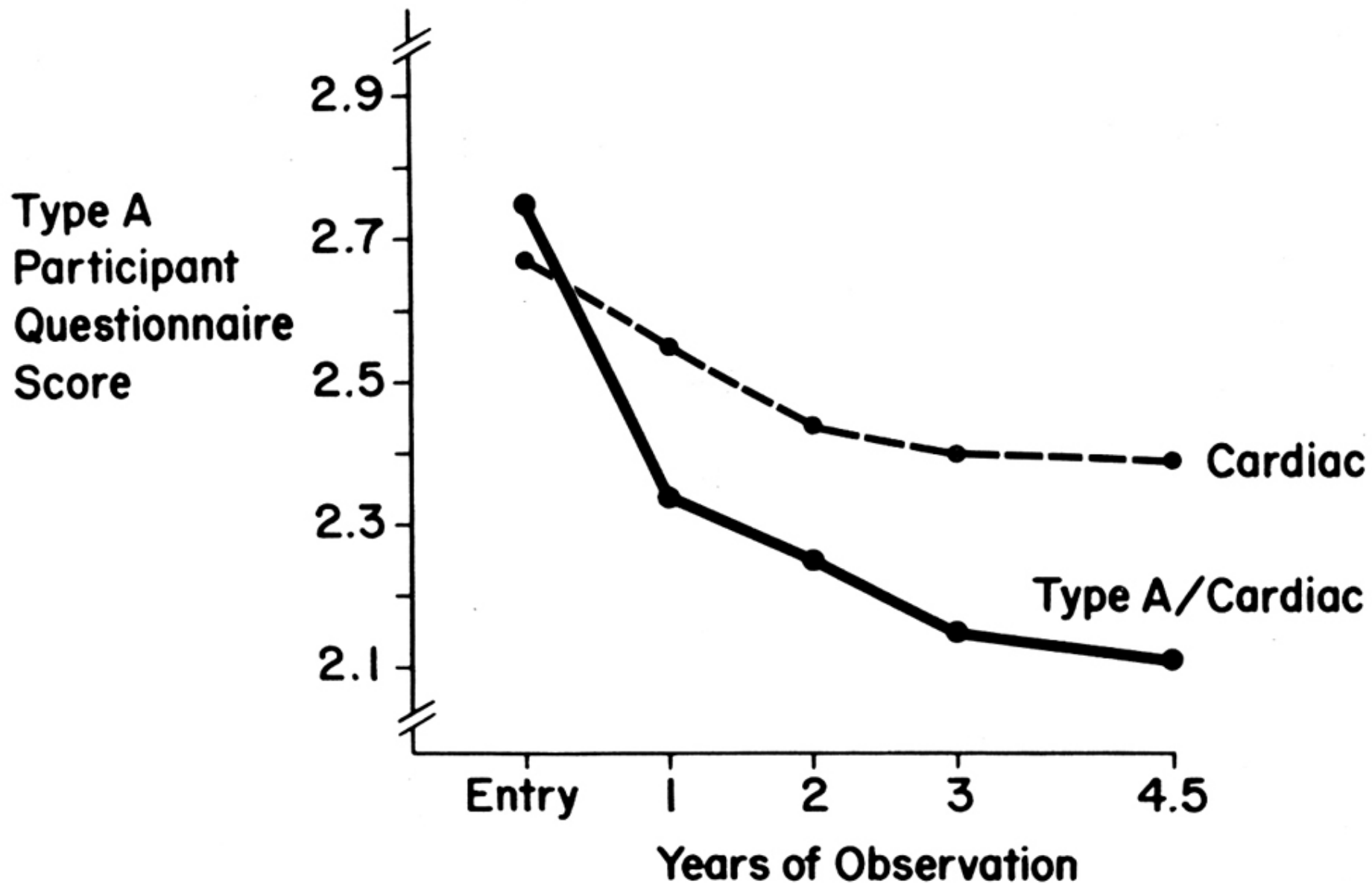
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7. Linger at table

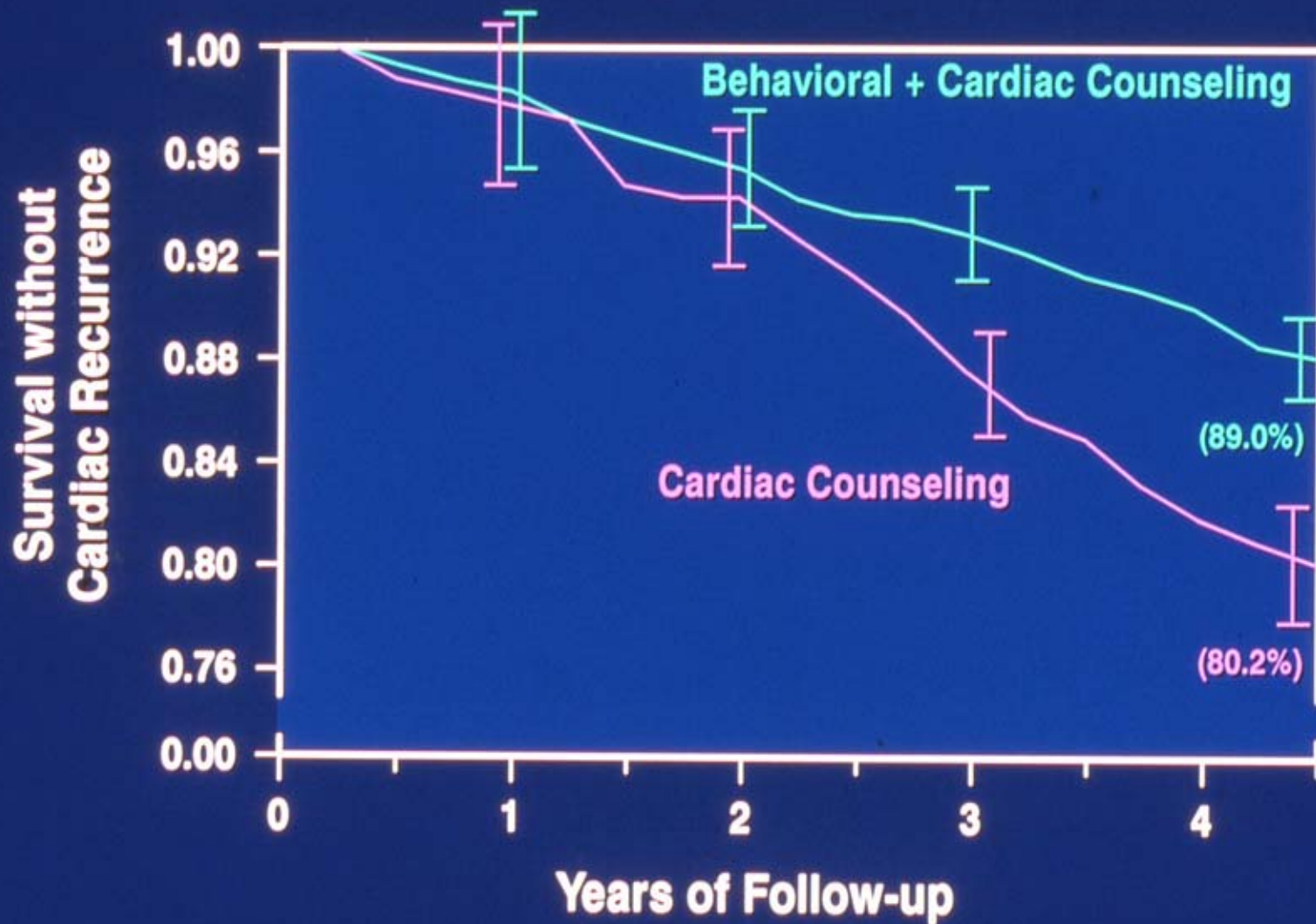
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# help

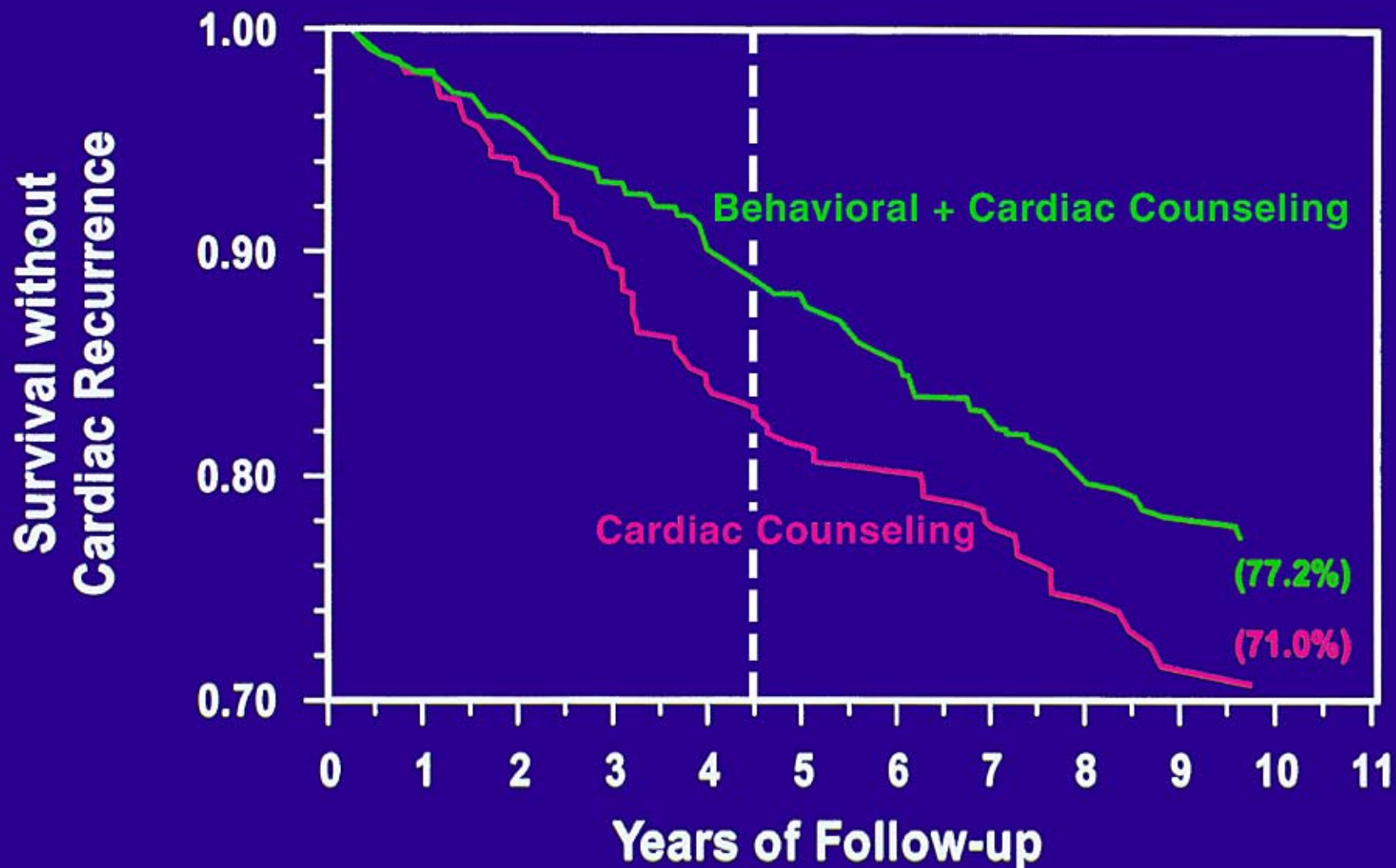




# Cardiac Recurrence at 4.5 Years



# Cardiac Recurrence at 8.5 Years



# Impact of RCPP Intervention on Psychosocial Risk Factors

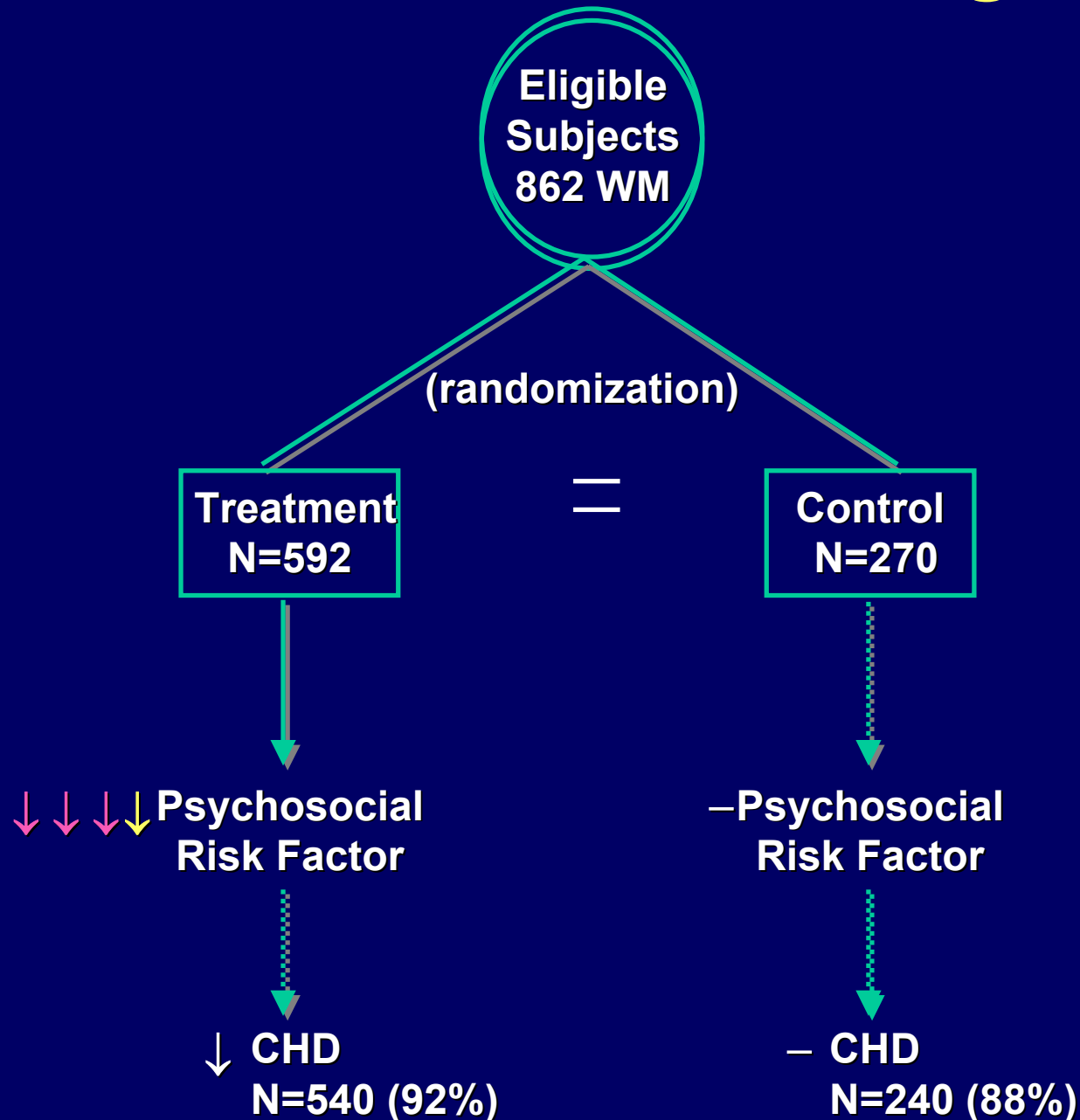
	Improved at End of Treatment	Improvement Predicted Subsequent CHD Events
Type A Behavior	***	ns
Hostility	***	ns
Anger	***	ns
Impatience	***	ns
Life Satisfaction	***	ns
Self-Efficacy at Managing Stress	***	*
Social Support	***	ns
Depression	***	**

\*\*\*  $p < 0.001$

\*\*  $p < 0.01$

\*  $p < 0.05$

# RCPP Clinical Trial Design



# WHAT WE LEARNED

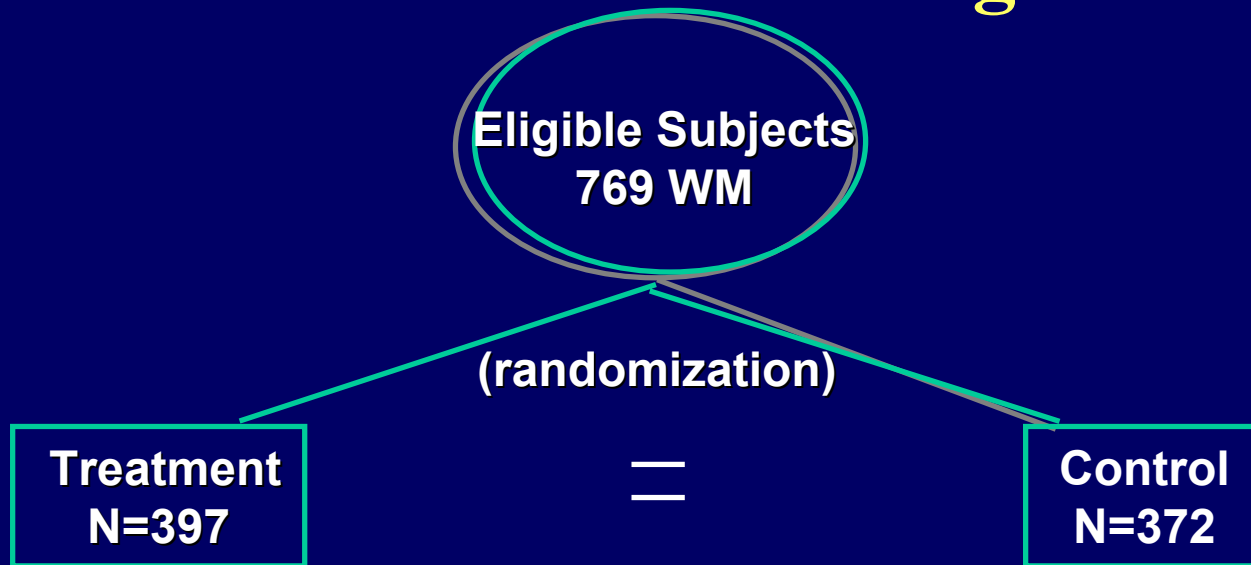
- Value of strong intervention.
- Many things can change during the course of a behavioral intervention. The intended treatment target may not be the real mechanism of effectiveness.

# The Ischemic Heart Disease Stress Monitoring Trial 1983-1986

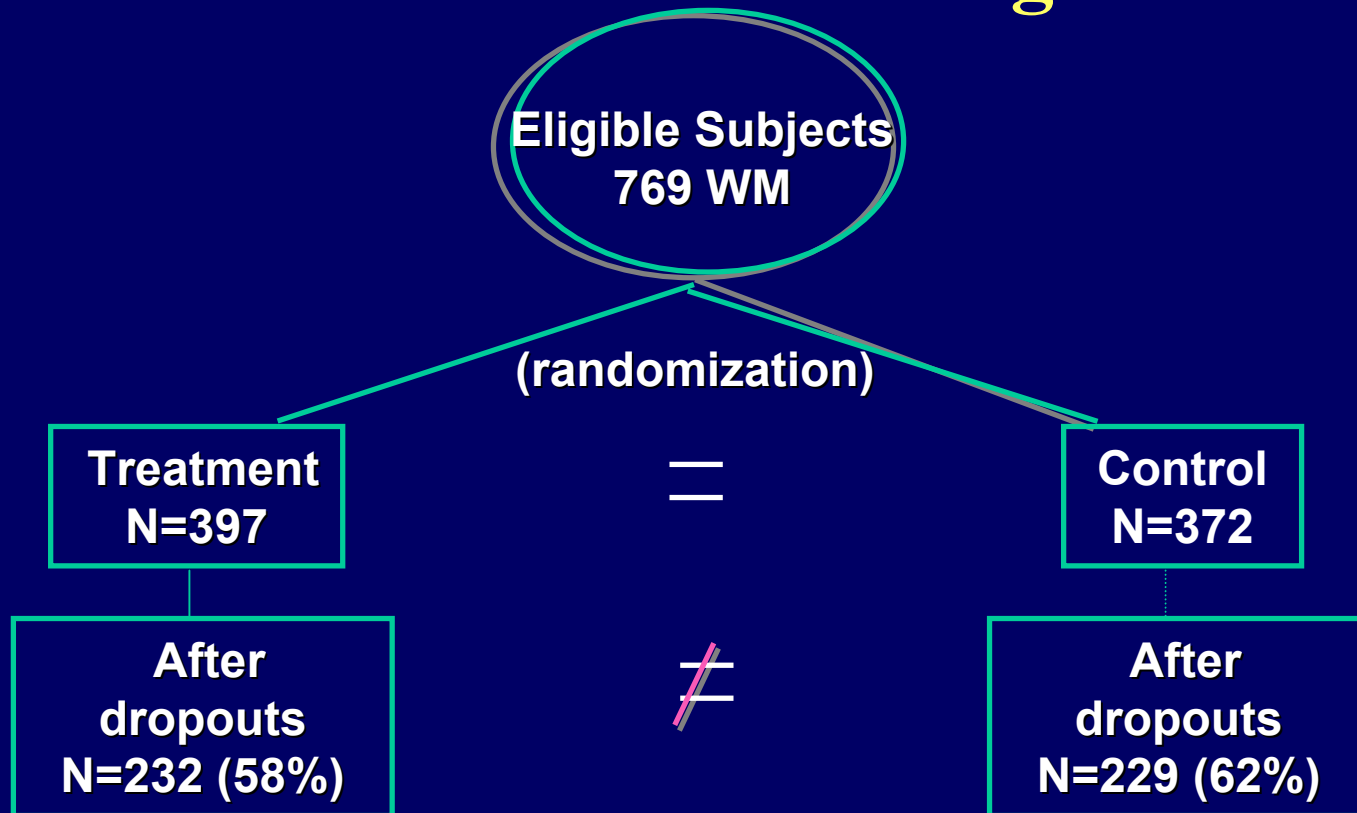
Principal Investigator: Nancy Frasure-Smith, PhD

**PURPOSE:** To determine if the provision of emotional support at a time of high vulnerability to stress can produce a reduction in the rate of nonfatal MI or coronary death in male post-MI patients.

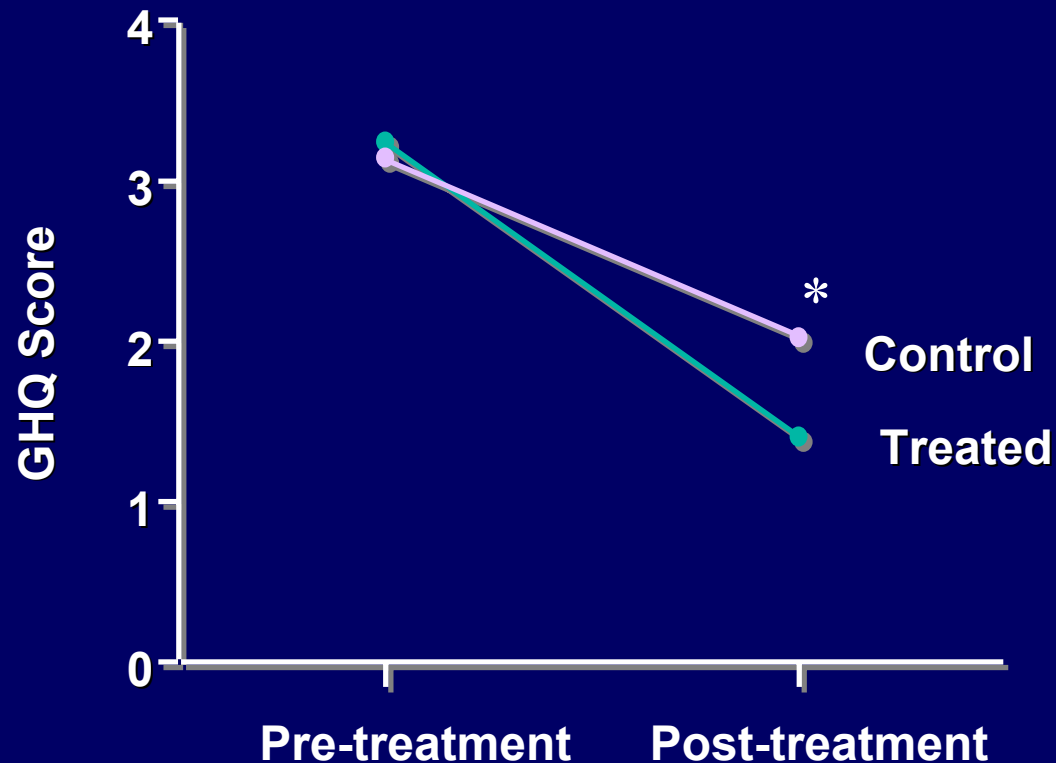
# IHD Stress Monitoring Clinical Trial Design



# IHD Stress Monitoring Clinical Trial Design



# Reduction in Distress at 1-Year Follow-up



\*  $p < 0.05$

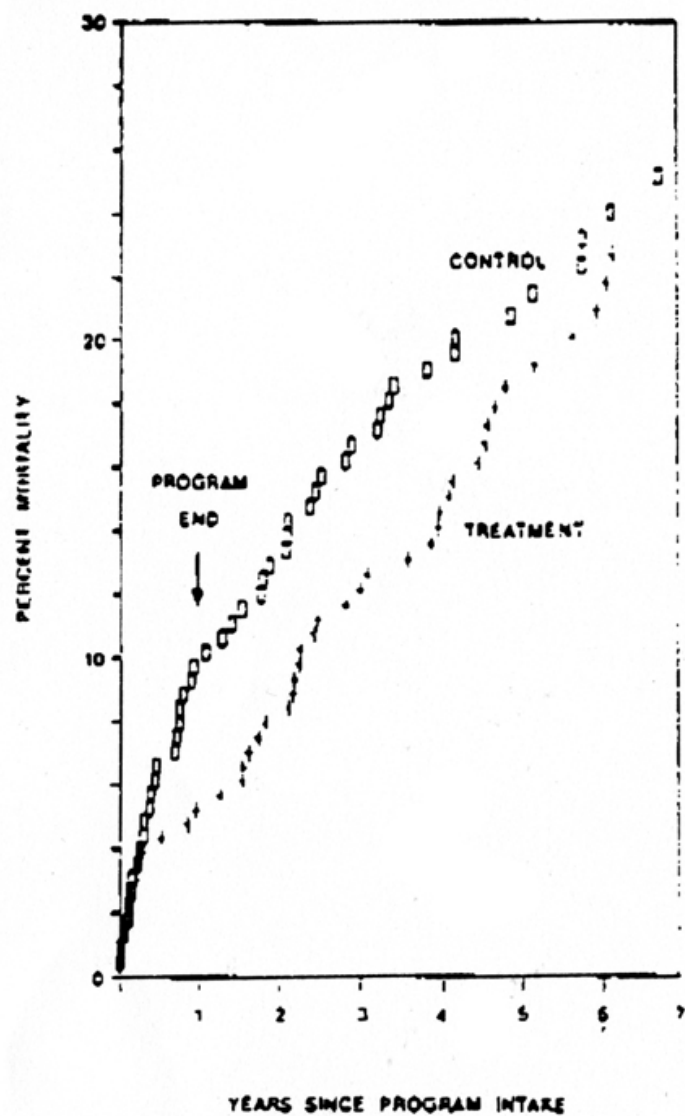


Fig. 1. Cumulative cardiac mortality in the treatment and control groups.

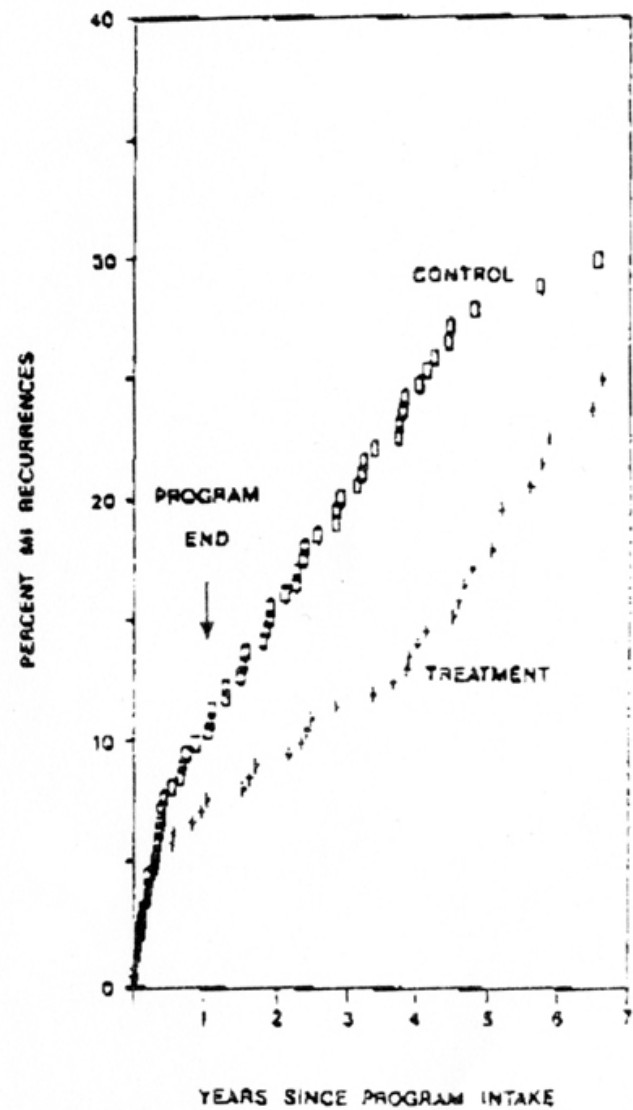
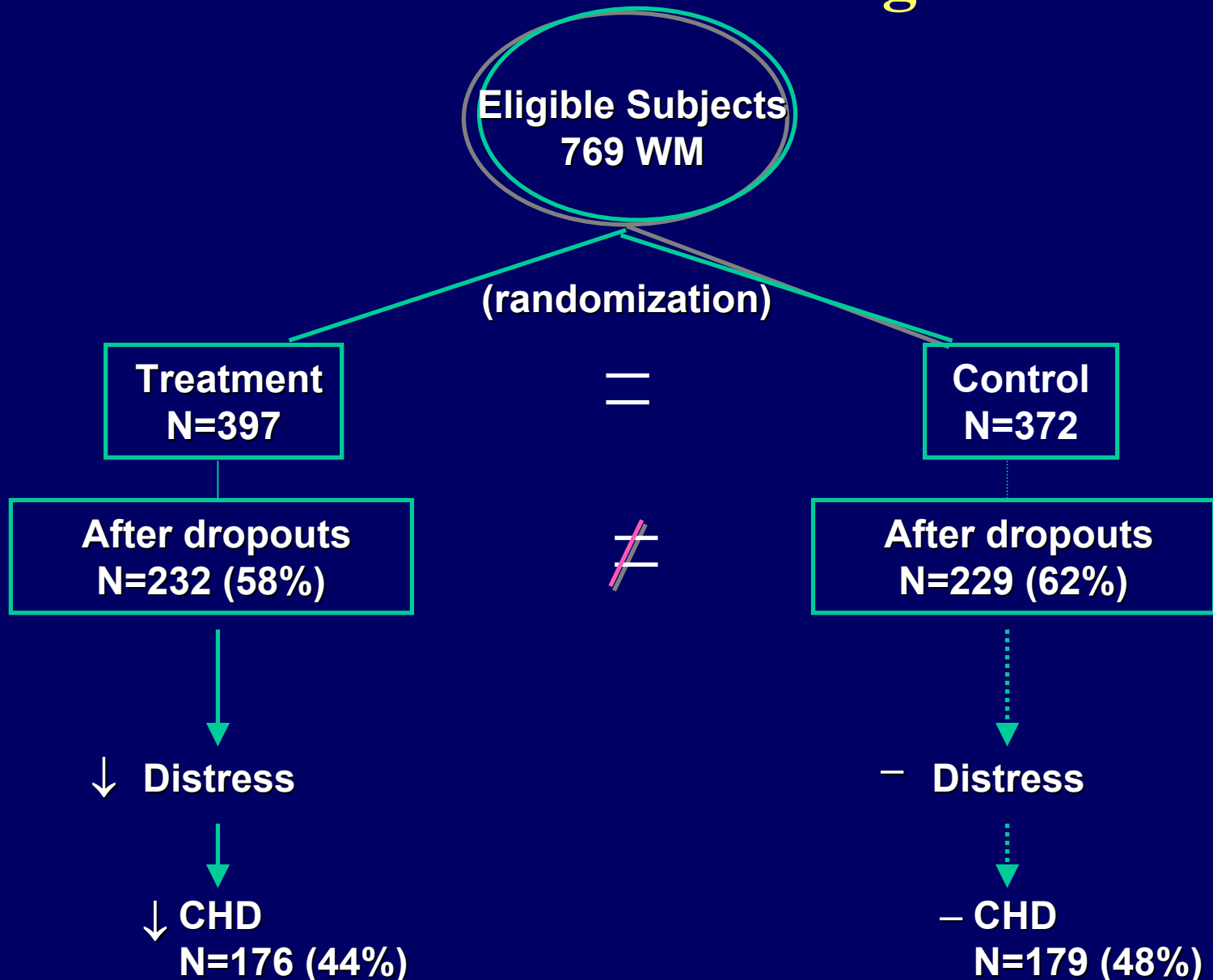


Fig. 3. Cumulative MI recurrences in the treatment and control groups.

# IHD Stress Monitoring Trial: Baseline Comparability

	Treatment	Control
Education	↑	↓
Occupation: White Collar	↑	↓
Income	↑	↓

# IHD Stress Monitoring Clinical Trial Design



# WHAT WE LEARNED

Guard the randomization  
throughout the trial.

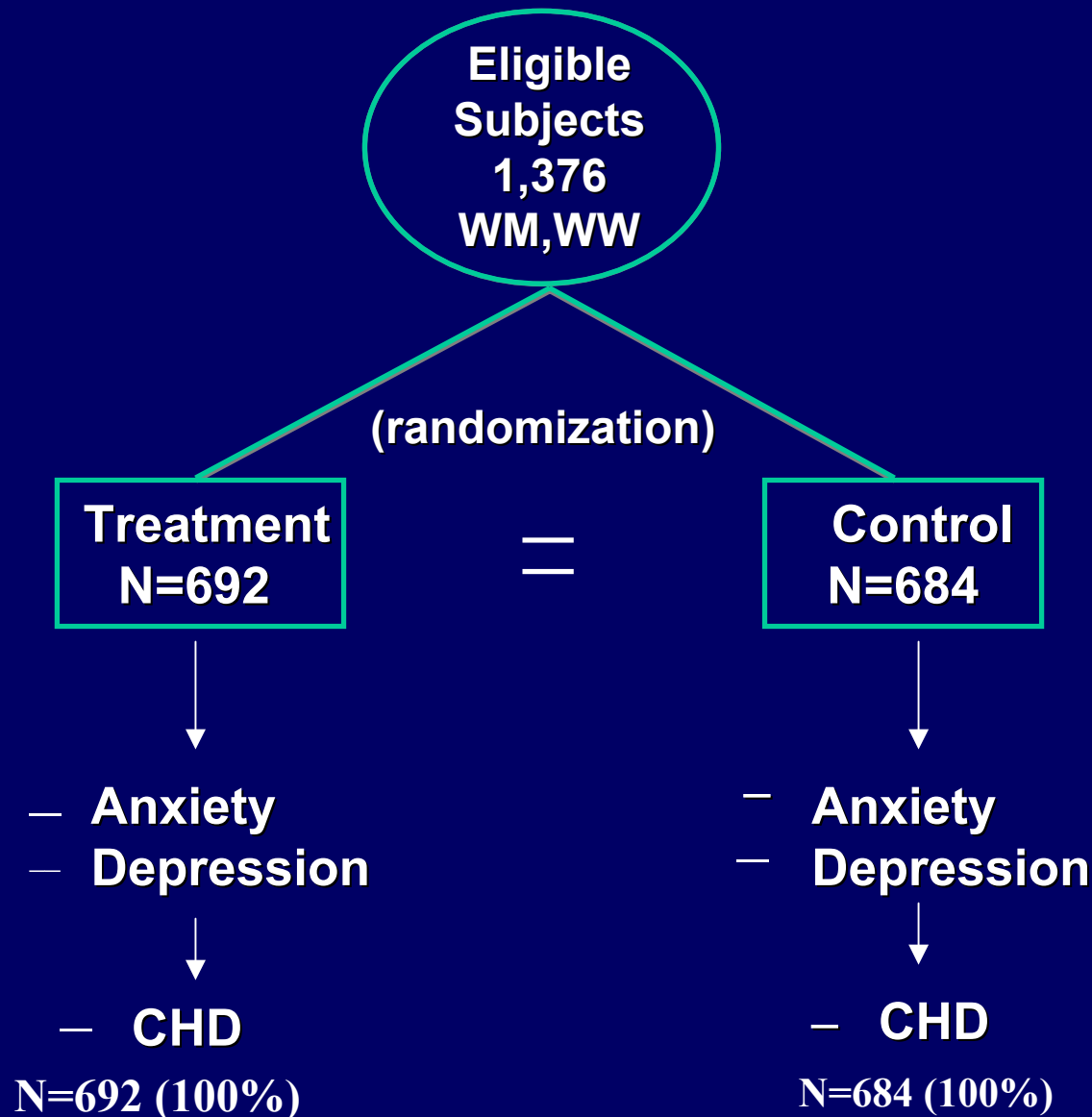
# Montreal Heart Attack Readjustment Trial (M-HART) 1992-1997

Principal Investigator: Nancy Frasure-Smith, PhD

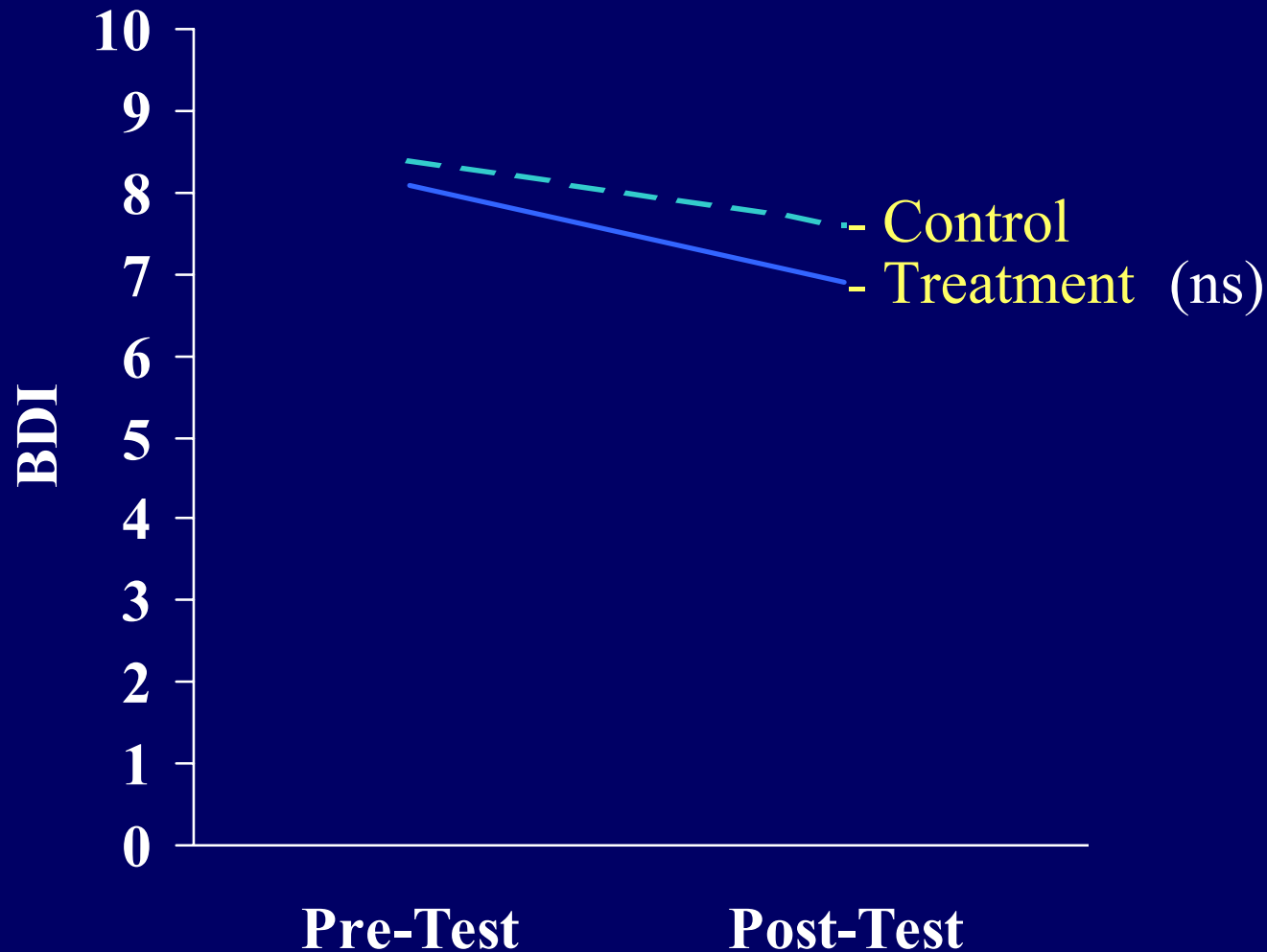
## PURPOSE:

- To replicate findings that provision of emotional support at a time of high vulnerability to stress can reduce incidence of cardiac death or nonfatal MI in *male* post-MI patients.
- To determine benefits of treatment in *female* post-MI patients.

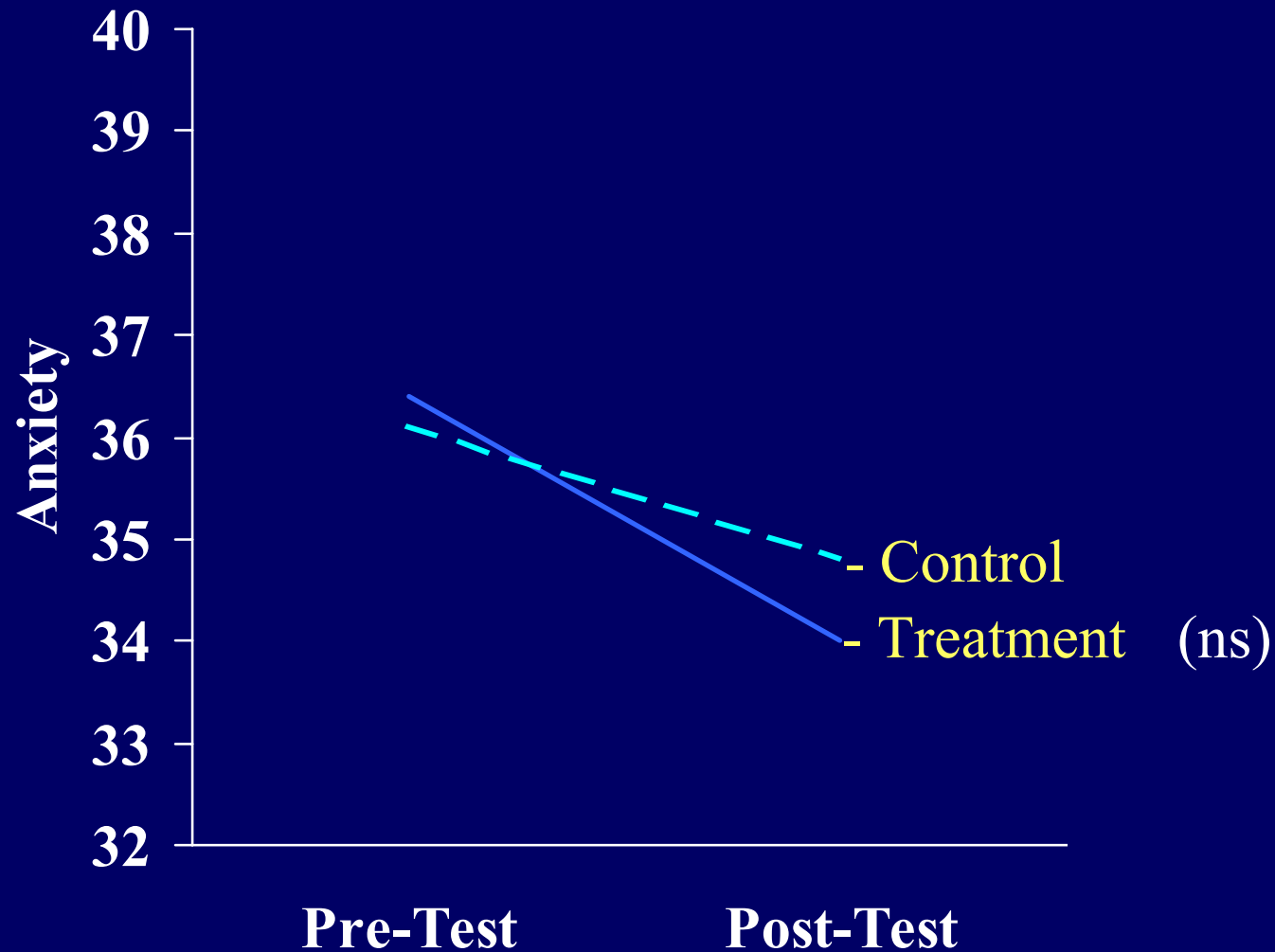
# M-HART Clinical Trial Design

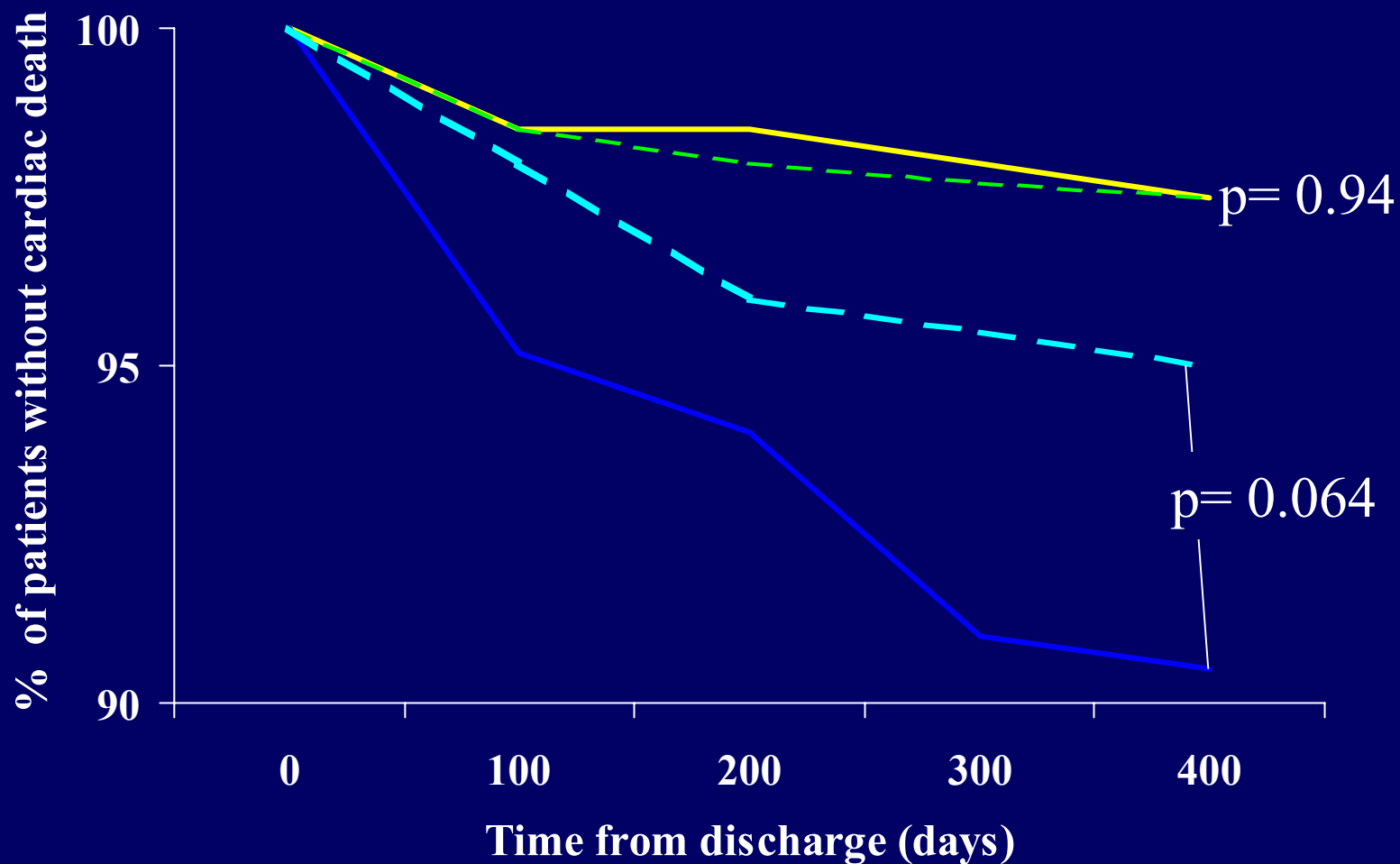


# M-HART Change in Depression



# M-HART Change in Anxiety





— Intervention men (n=458)	- - - Control men (n=445)
— Intervention women (n=234)	- - - Control women (n=239)

# WHAT WE LEARNED

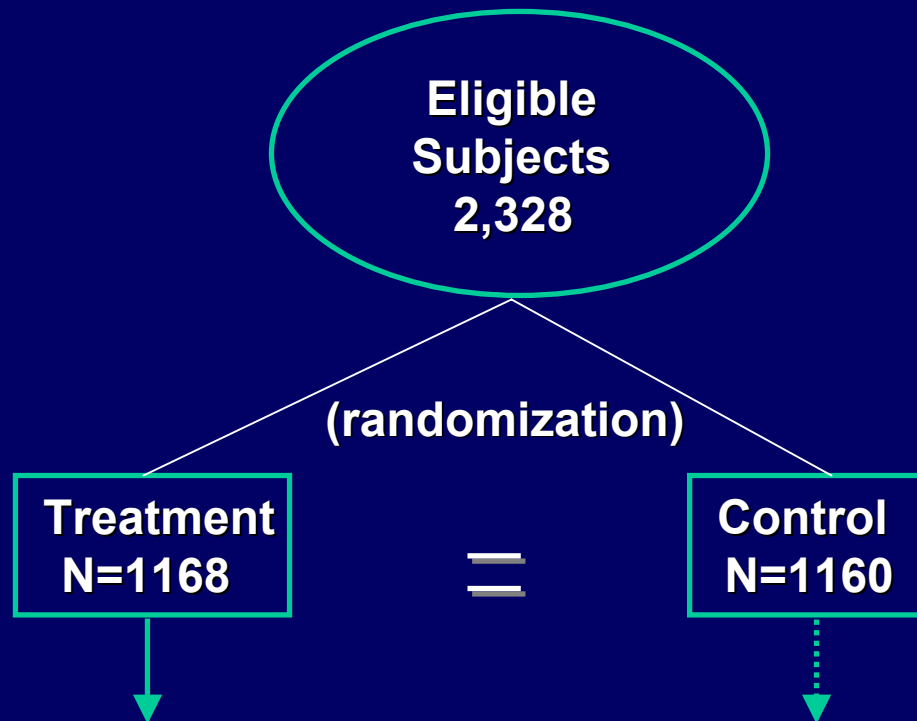
- Replication of treatment benefits is essential to minimize effects of bias.
- Behavioral treatments *can* harm.

# Jones and West Rehabilitation Program 1990-1996

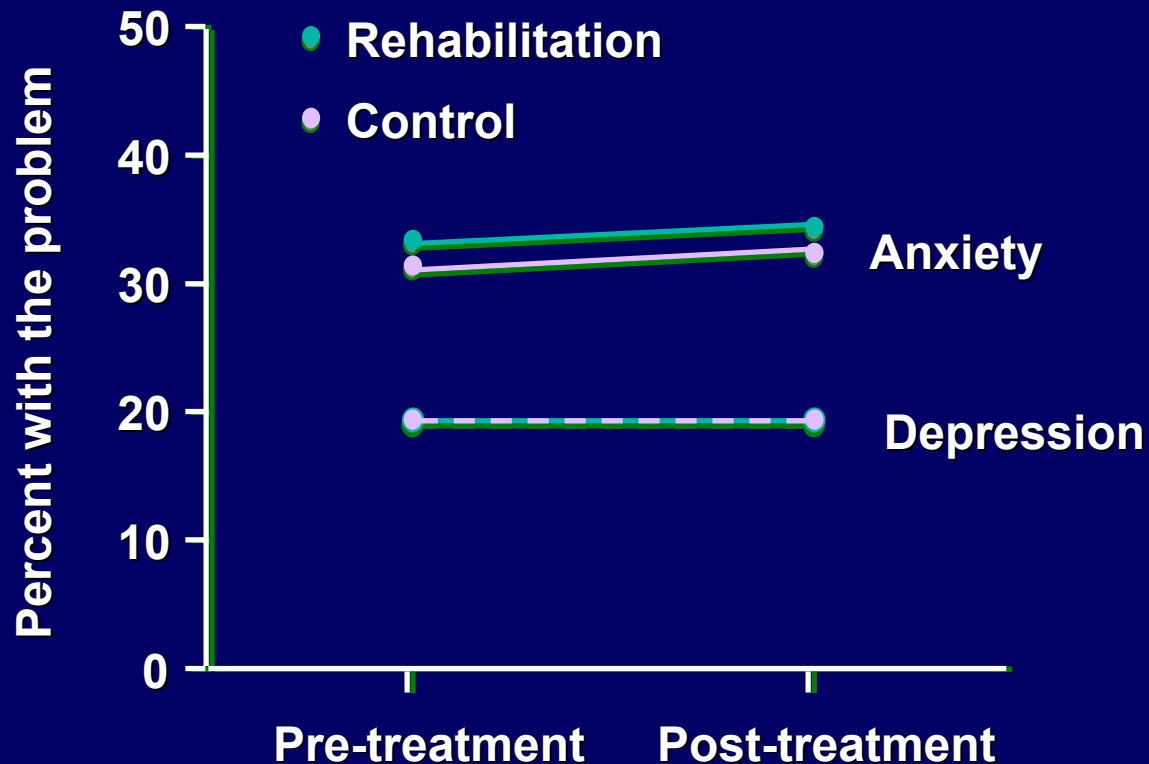
Principal Investigator: DA Jones, MD

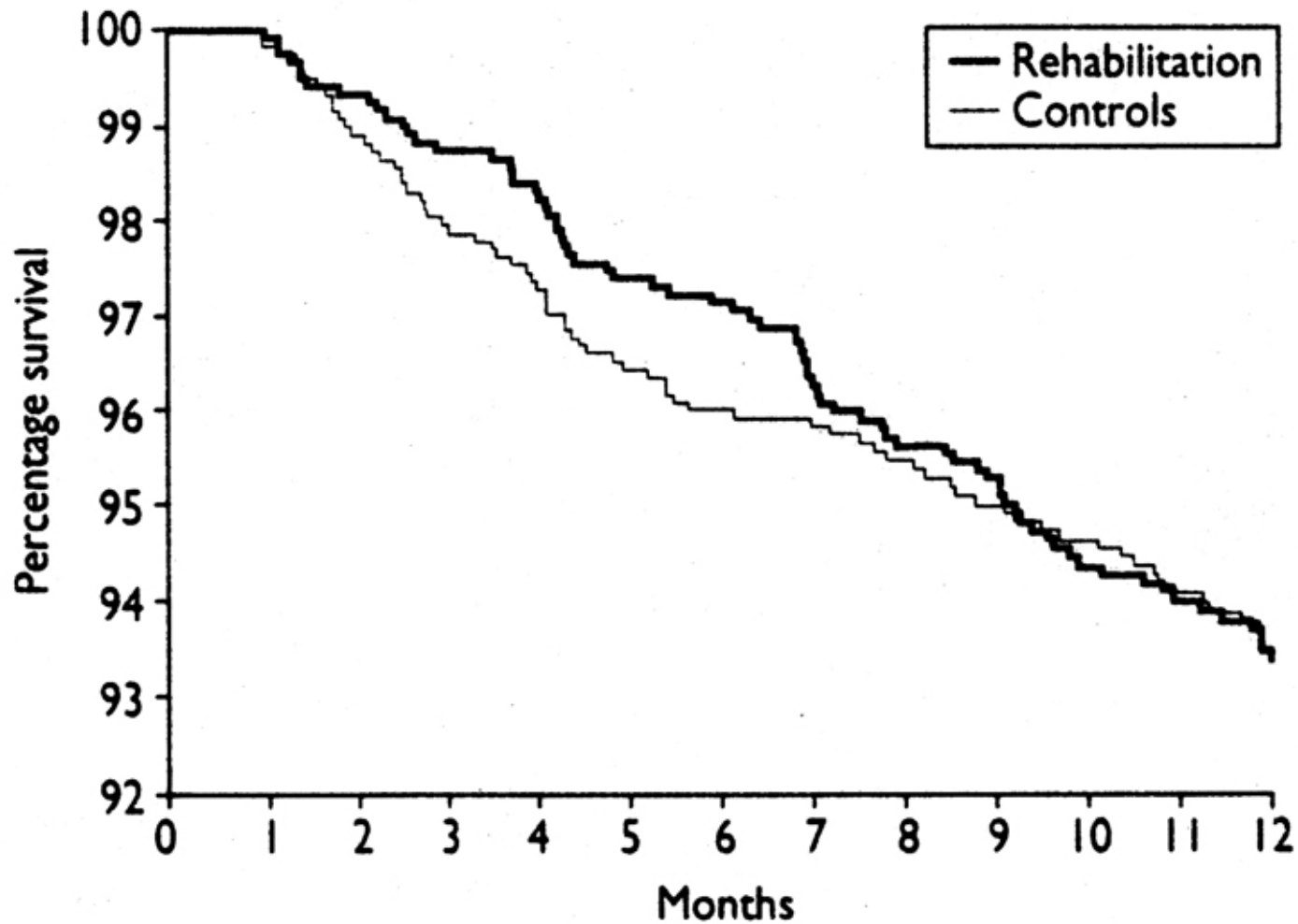
**PURPOSE:** To determine the impact of a 7-week cardiac rehabilitation program on mortality in post-MI patients.

# Jones & West Rehabilitation Program Clinical Trial Design



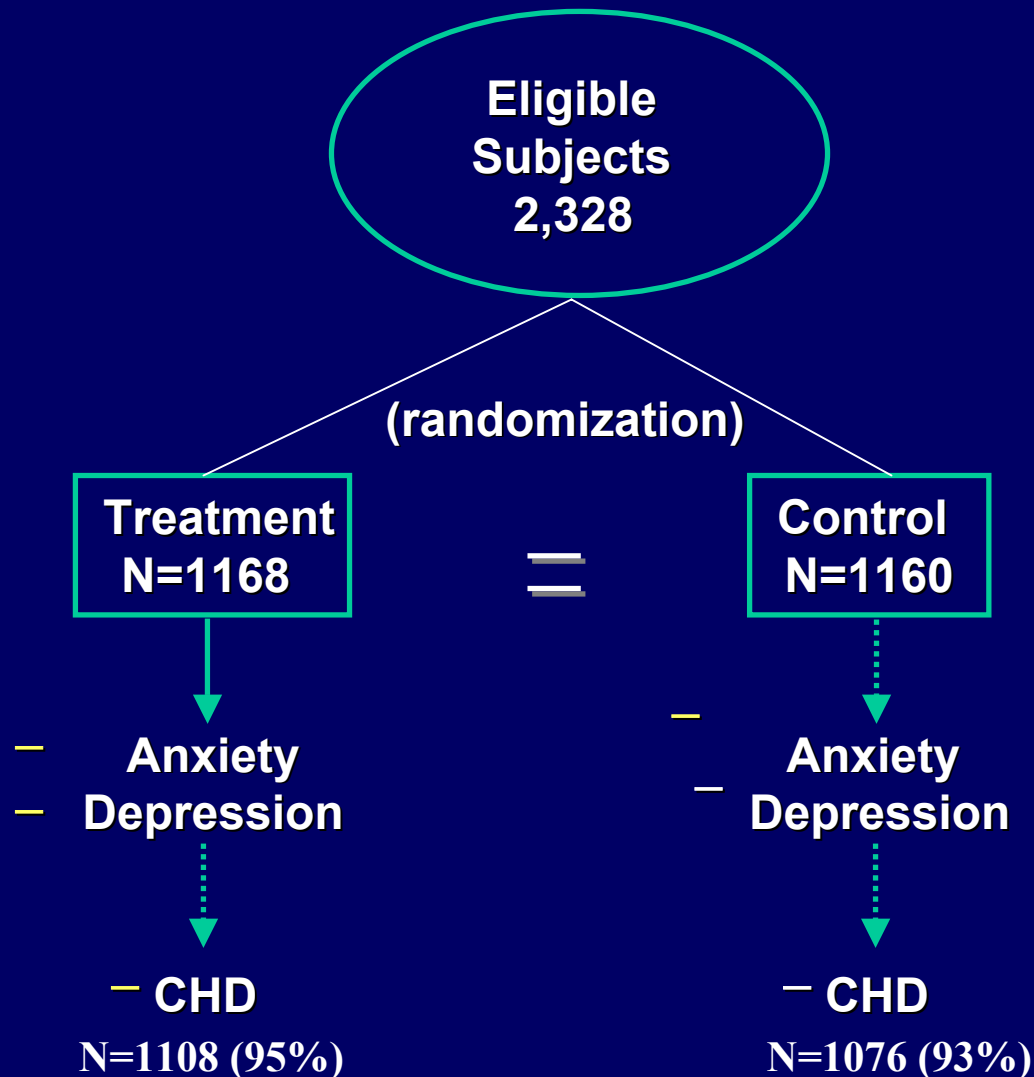
# Reduction in Anxiety and Depression at 6-Month Follow-up





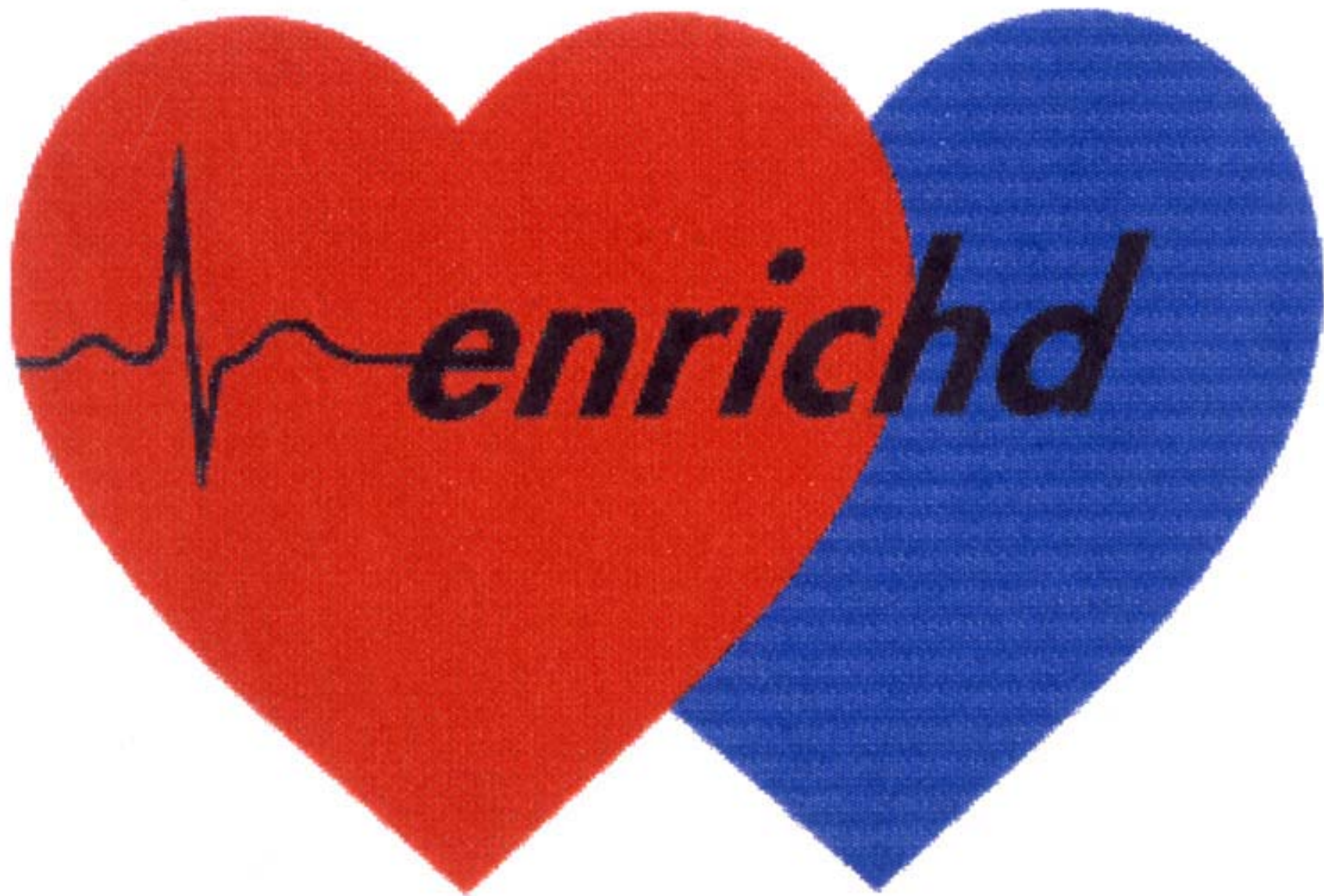
**Fig 2—***Percentage survival after 28 days in rehabilitation and control groups*

# Jones & West Rehabilitation Program Clinical Trial Design



# WHAT WE LEARNED

Pilot the intervention to insure that  
it can improve behavioral targets  
*before* undertaking a trial.

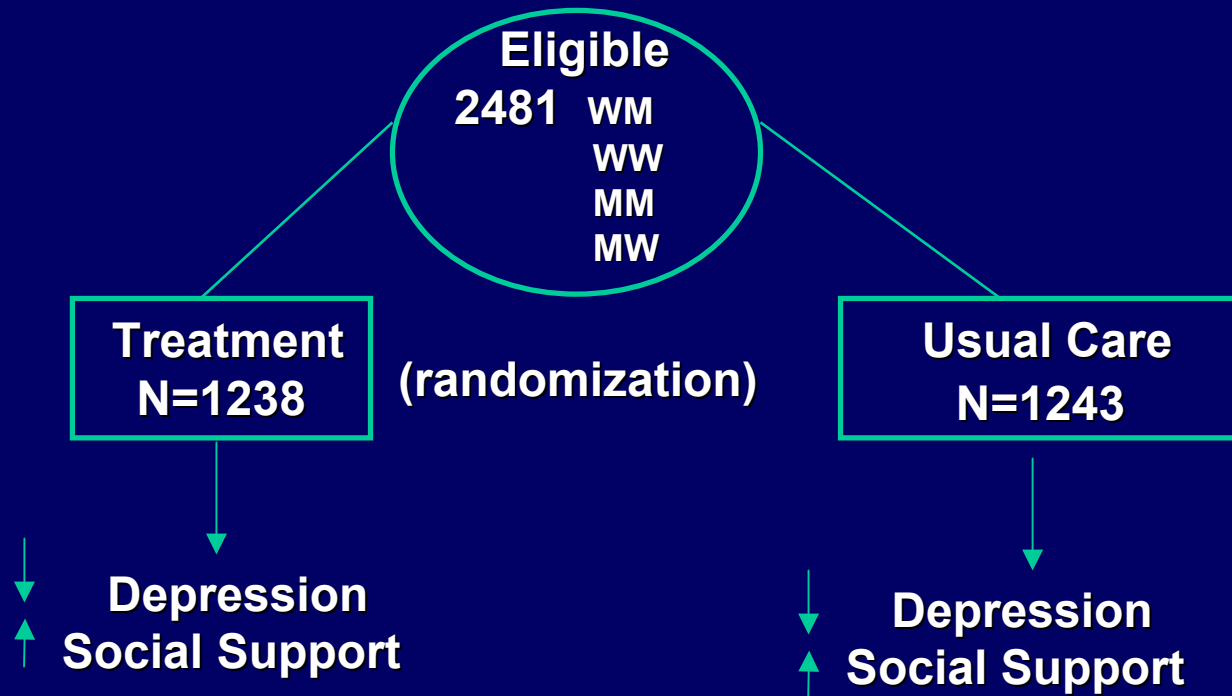


# Enhancing Recovery in Coronary Heart Disease (ENRICHD) Trial 1996-2003

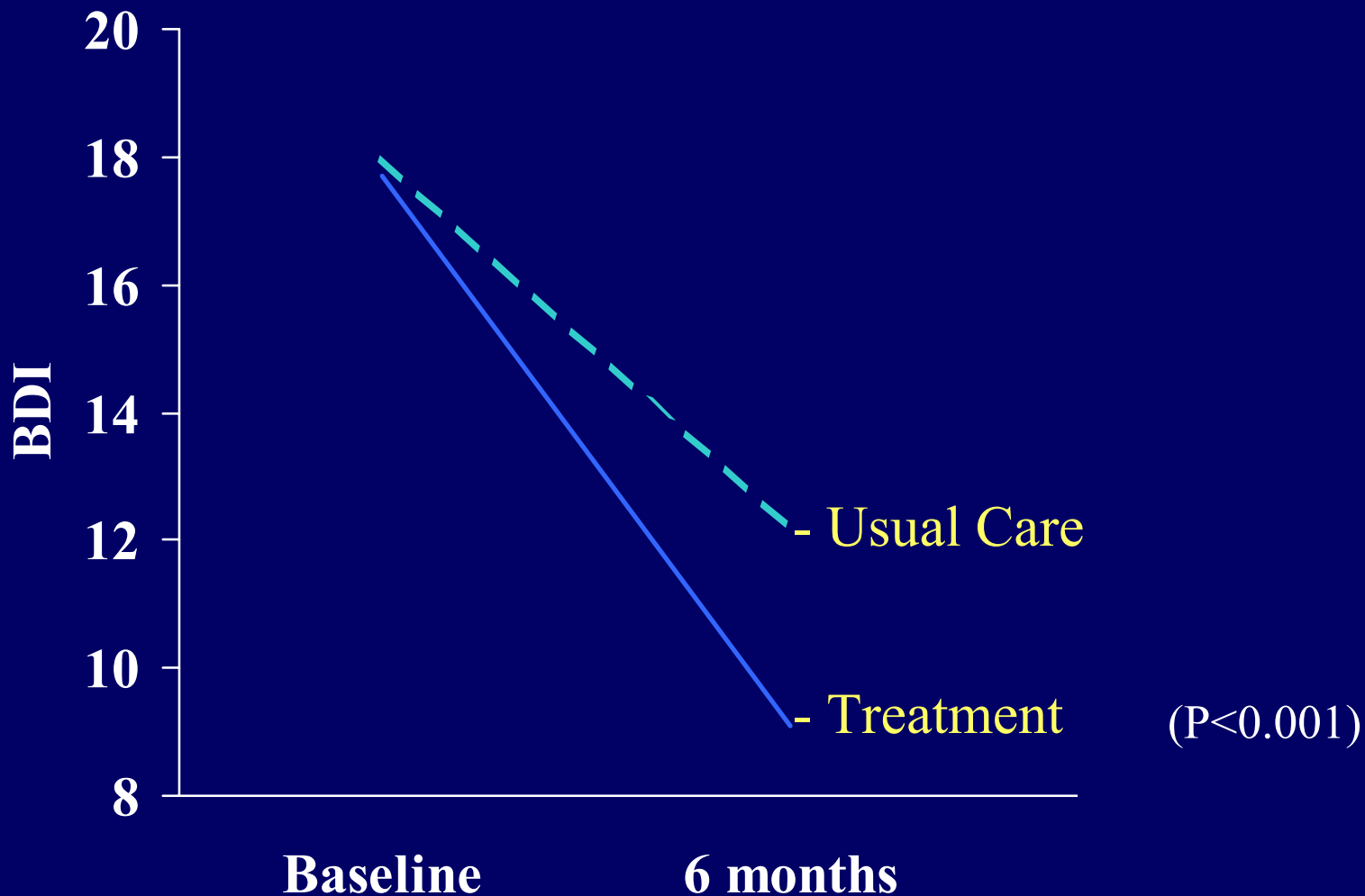
Principal Investigator: The ENRICHD Investigators

PURPOSE: To determine if a 6-month treatment for depression and/or low social support early after an MI will reduce mortality or nonfatal MI.

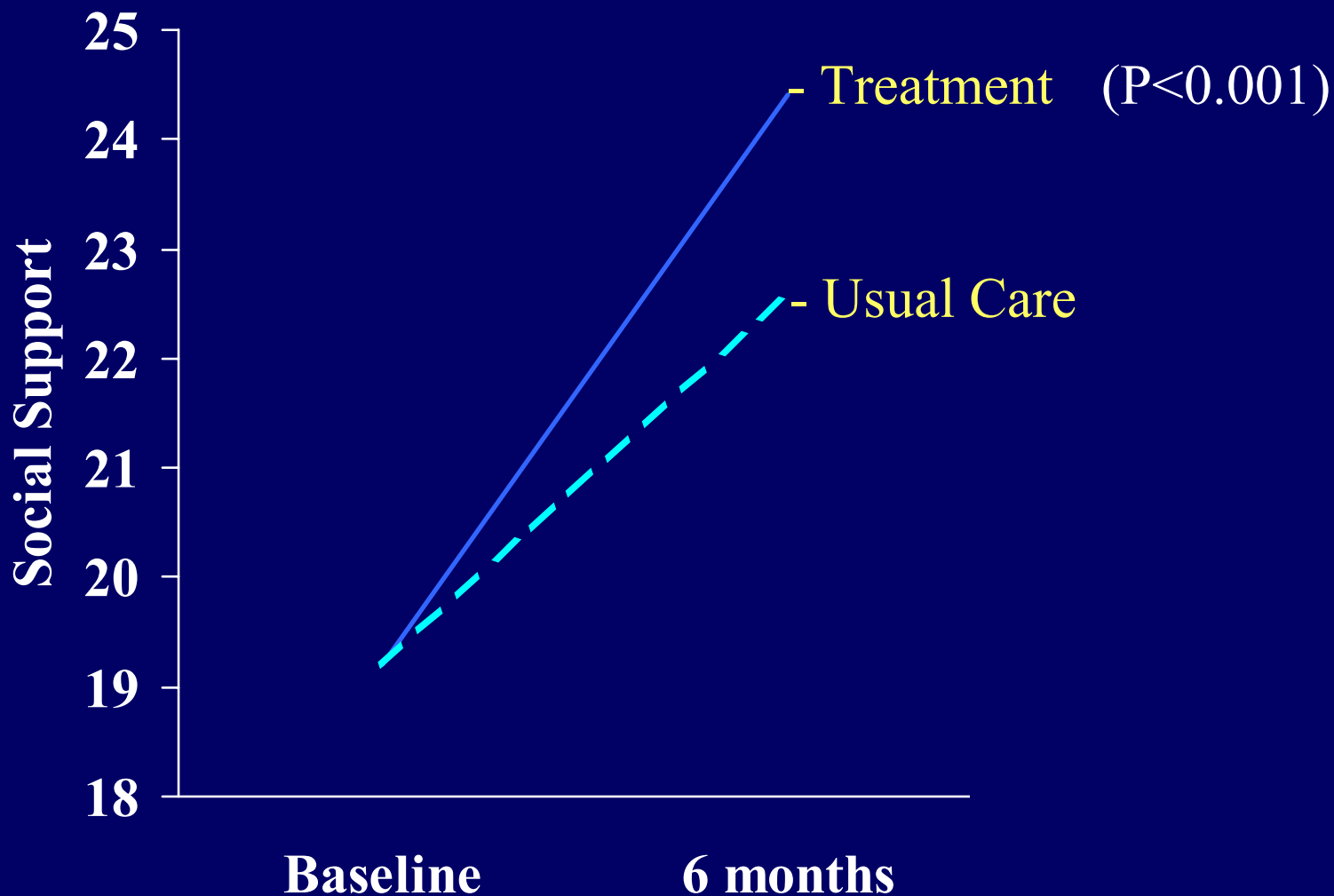
# ENRICHD



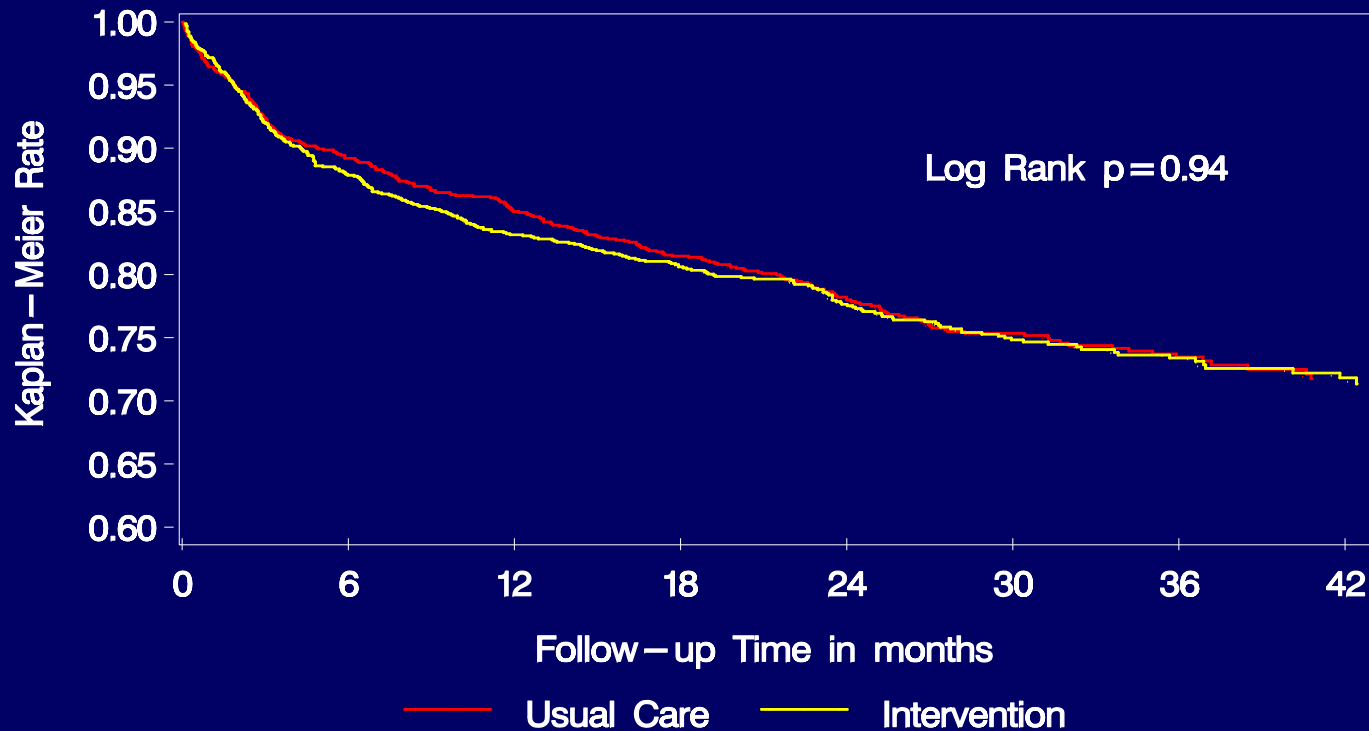
# ENRICHD: Change in Depression



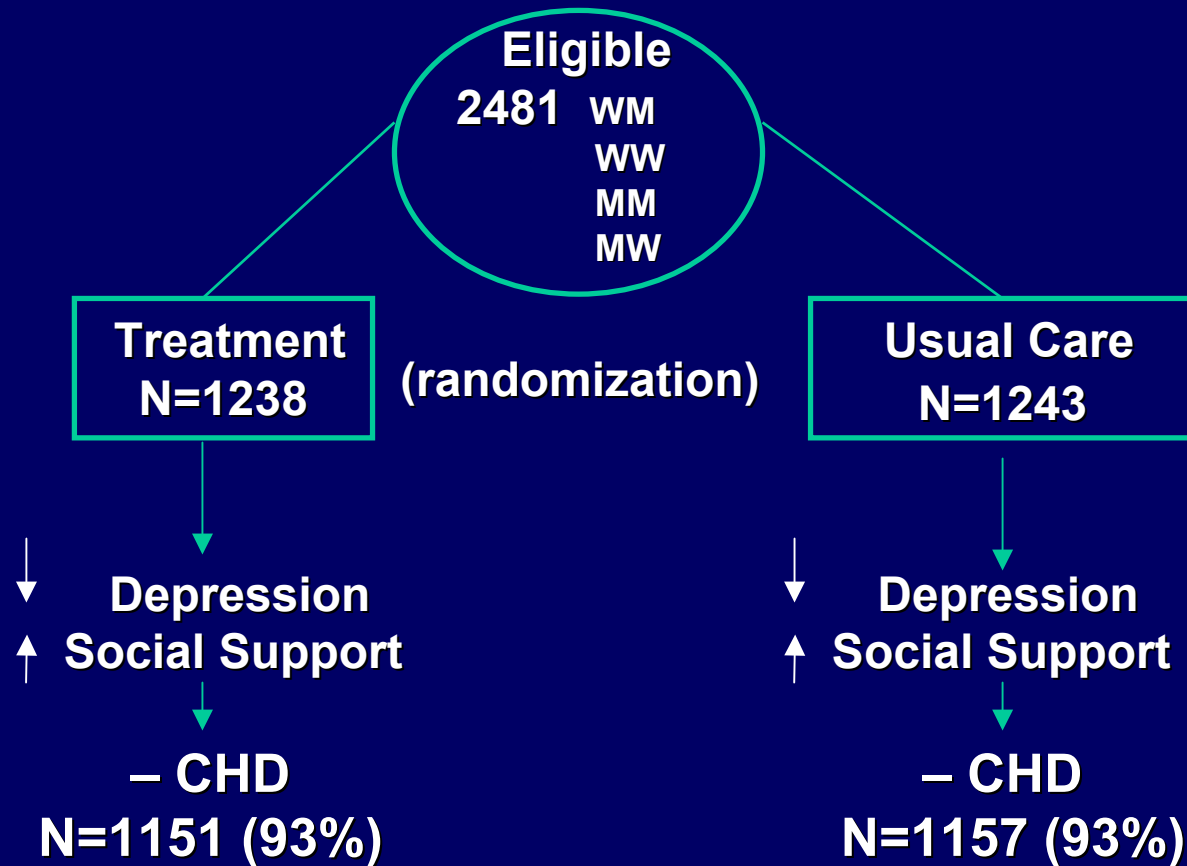
# ENRICHD: Change in Social Support



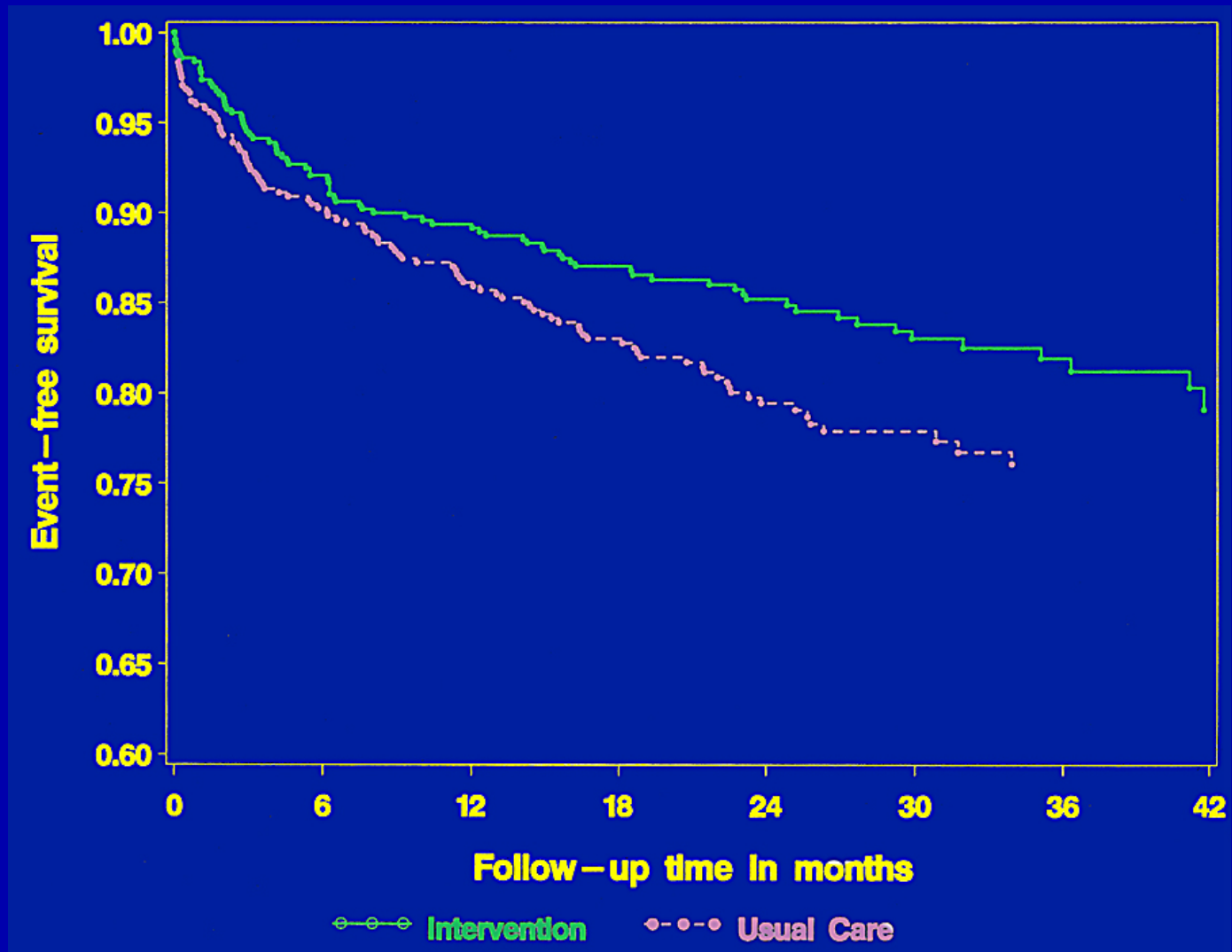
# Kaplan-Meier Survival Curves



# ENRICHD



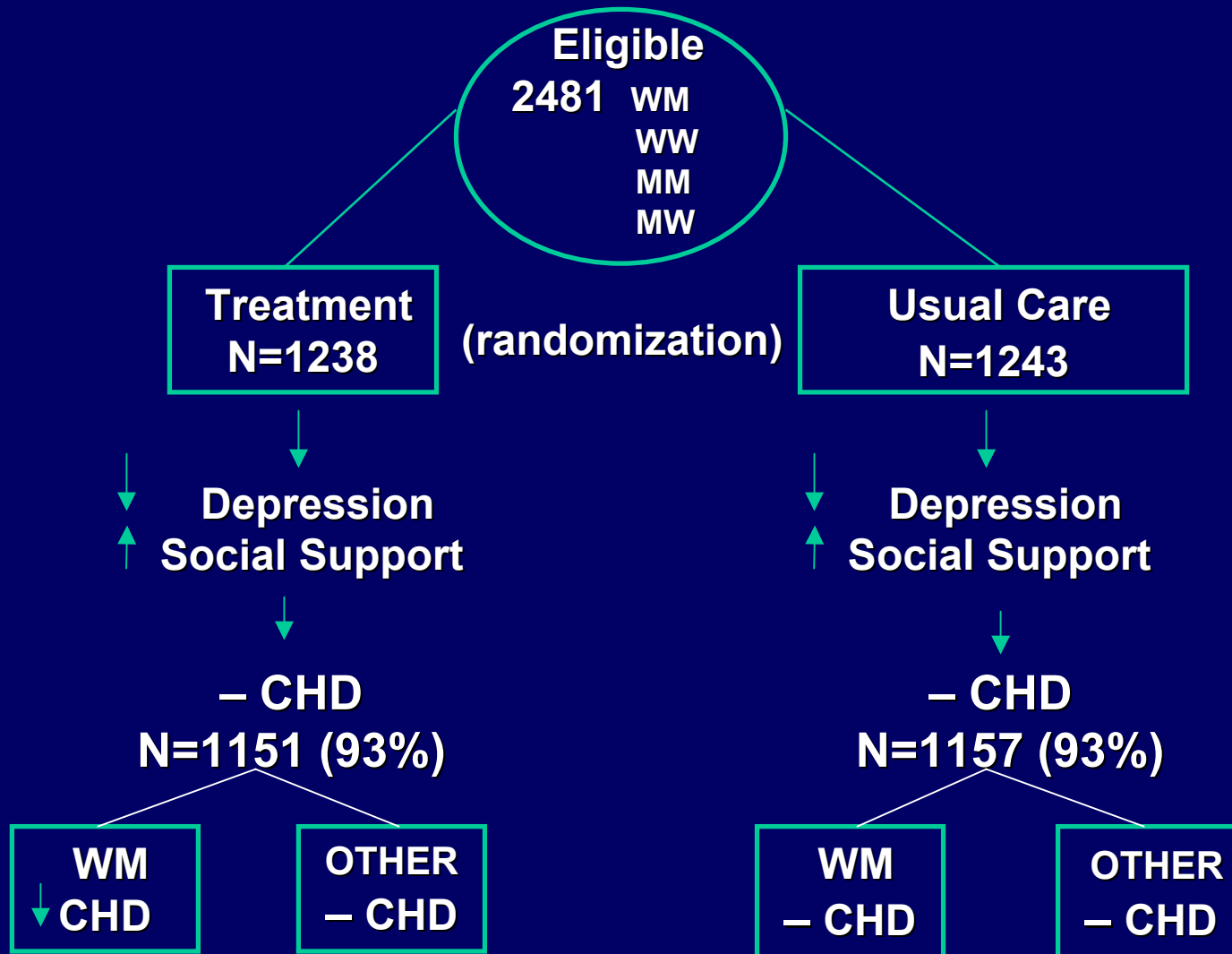
# Impact of Treatment for White Males



# ENRICHED: Primary Endpoint



# ENRICHD



# WHAT WE LEARNED

- Value of strong intervention.
- One size may not fit all.  
Understand cultural variability in response to treatment.

“An error doesn’t become a mistake  
until you refuse to correct it .”

- OrlandoA. Battista

Heart Failure  
Adherence &  
Retention Trial

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# Heart Failure Adherence and Retention Trial (HART) 2001-Present

Principal Investigator: Lynda H. Powell, PhD

**PURPOSE:** To determine if self-management training can improve adherence and prevent hospitalization or death in patients with heart failure.

# ISSUE: Choice of Appropriate Control Group

## **Usual Care:**

To determine treatment efficacy over the standard of care.

## **Attention Control:**

To determine whether treatment was efficacious over the simple provision of attention.

# ISSUE: Delay Time Between Randomization and Start of Treatment

Logistical difficulties in the formation of groups result in delay before start of treatment. Focused recruiting and case management of “waiters” is needed.

ISSUE: Poorer attendance early in treatment in the disadvantaged minorities results in differential exposure to full treatment package.

Make-up sessions for missed meetings in later phase of treatment may minimize differential exposure to treatment by ethnicity.

# Summary

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1. A behavioral intervention can harm. Understand the beliefs and attitudes of all targeted subgroups including women, minorities, and people of lower educational levels.
  2. Pilot the intervention first. Be completely confident in its efficacy before undertaking a clinical trial of its impact on health. Be particularly sensitive to gender and minority variation in response.
  3. Randomize and guard the randomization throughout the trial. Randomization provides the best control for the measured and unmeasured confounders available.
  4. Be objective and humble. Science moves slowly. Remain open to the possibility that the behavioral intervention:
    - will not work;
    - may work due to unintended mechanisms;
    - will be misinterpreted;
    - will not be accepted in the larger community if it does work.
-